EXHIBIT C

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

BOEHRINGER INGELHEIM INTERNATIONAL GMBH and BOEHRINGER INHELHEIM PHARMACEUTICAL, INC. Plaintiffs, v. BARR LABORATORIES, INC., Defendant.	Civil Action No. 05-0700 (KAJ)

EXPERT REPORT OF PROFESSOR PAUL A. BARTLETT, Ph.D.

A. INTRODUCTION

1. I am a Professor of Chemistry, Emeritus, at the University of California, Berkeley. I began teaching at Berkeley in 1973 and was Chair of the Department of Chemistry from 1996 to 2000.

2. I obtained my A.B. in Chemistry from Harvard University in 1969 and my Ph.D. in Organic Chemistry from Stanford University in 1972. From 1972 through 1973 I was a postdoctoral fellow at the University of California, San Diego. I have attached my curriculum vitae and a list of my publications as Exhibit A.

3. In addition to fulfilling my teaching duties as a Professor at Berkeley, I led a research group in the field of bioorganic chemistry and synthetic organic chemistry. Under my direction, 63 students have received their Ph.D. degrees, more than 75 postdoctoral fellows and visiting scientists have carried out advanced research, and countless undergraduate students have had their first exposure to original research. Some of my coworkers went into academe, while

most have gone on to successful industrial careers in research and development in the pharmaceutical, biotech, and agrochemical fields.

4. I have served as the director of the Center for New Directions in Organic Synthesis since I founded the Center in 1999, while I was department Chair. The role of this Center is to improve the interactions between industry and academe in this field, thus improving the training our students receive and facilitating industrial support for laboratory renovation for junior faculty.

5. As a consequence of my research interests and accomplishments, I have had the opportunity to consult broadly with industry across many of my fields of interest and I lecture extensively on drug design. I first began working as a consultant in 1979, for the Bristol-Myers Company, consulting for both its research and development divisions. The former group was concerned with the discovery of new medicinal agents, and the latter was charged with finding efficient and workable methods for their manufacture. I had similar interactions with the corresponding divisions at Schering-Plough when I consulted for it from 1984-1996. I have consulted for companies engaged in medicinal chemistry, in agrochemistry, in biotechnology, and chemical software development. I also co-founded a successful start-up company engaged in drug discovery. Through these interactions, which are detailed in my curriculum vitae, I have had extensive opportunity to participate in the drug discovery and development processes in the industrial context.

6. I have co-authored more than 180 articles and abstracts in the field of organic chemistry, bioorganic chemistry, and drug design, and I am named as co-inventor on several United States patents. The list of publications that I have written or to which I have contributed is attached to my curriculum vitae.

7. I am a member of a number of technical societies, serve on the editorial advisory boards of several technical journals, and have chaired a number of technical conferences. Many of these professional positions have been in the field of drug discovery. I have also received several awards in my field, including, for example, the Cope Scholar Award from the American Chemical Society in 1990. I was also elected a Fellow in the American Academy of Arts and Sciences in 1994. Early in my career I received the Stuart Pharmaceuticals Award and an Eli Lilly Young Scientist Award, in recognition of my accomplishments in research and its relevance to the pharmaceutical industry.

8. I am very familiar with the field of organic synthesis, namely that branch of organic chemistry that involves the preparation of more complex molecules from less complex molecules. I received my Ph.D. training in this field, it has been an important component of my own research throughout my career, and it has been an area in which I have consulted extensively for industry. I have an understanding not only of synthetic operations on the laboratory scale, but also of how these operations are carried out as large-scale manufacturing processes.

9. On the basis of my education and the experience described above, I believe I am qualified to give the opinions set out herein.

B. MANDATE

10. I have been asked to provide a tutorial on drug development and a discussion of the Boehringer inventors' research that led to the invention claimed in the U.S. Patent No. 4,886,812 (" the '812 Patent), particularly the compound called pramipexole.

11. In addition, I have been asked to respond to the opinions offered by Dr. Eric Anslyn, an expert retained by Defendant Barr Laboratories ("Barr") in this matter. In particular, I have been asked to provide an opinion as to whether the German priority applications adequately describe and enable one of ordinary skill in the art to synthesize certain compounds encompassed by the '812 Patent.

12. I have further been asked to provide an opinion as to whether the work performed at Eli Lilly & Company ("Lilly") by Dr. Bennett Laguzza and Mr. William Turner, Jr. constitutes invention of 2-amino-6-dipropylamino-4,5,6,7-tetrahydrobenzthiazole, 2-amino-6-di-methylamino-4,5,6,7-tetrahydrobenzthiazole, and 2-methylamino-6-di-methylamino-4,5,6,7-tetrahydrobenzthiazole prior to June 19, 1985, the date that Dr. Laguzza and Mr. Turner signed the declaration for Lilly's U.S. patent application in which it is claimed.

13. In preparing this expert report, I have reviewed the materials set forth in Exhibit B. I have also reviewed the expert report of Dr. Anslyn. In addition to those documents, the opinions I express in this report are based on my own personal knowledge of, and experience in, the areas of drug design and development.

C. SUMMARY OF OPINIONS

14. The discovery of a new drug is a difficult process that involves the intersection of many scientific disciplines. Enormous experimental effort is undertaken to identify biologically active lead compounds and optimize them for evaluation as drug candidates, lengthy and expensive testing is required to determine if these candidates are suitable for administration to man, and extensive clinical trials are carried out to determine if they are efficacious and safe. In short, drug discovery is a challenging process in which there is no guarantee of success. The

discovery and development of pramipexole as an effective pharmaceutical agent was no exception.

15. My analysis of the evidence concerning the work performed at Lilly by Dr. Bennett Laguzza and Mr. William Turner, Jr. shows that it does not constitute invention of 2-amino-6-dipropylamino-4,5,6,7-tetrahydrobenzthiazole, 2-amino-6-di-methylamino-4,5,6,7-tetrahydrobenzthiazole, and 2-methylamino-6-di-methylamino-4,5,6,7-tetrahydrobenzthiazole prior to June 19, 1985.

16. As I explain in detail below, I disagree with Dr. Anslyn's opinion that "that there is nothing in either of the German applications that discloses implicitly or explicitly to the skilled artisan, any starting material, intermediate, or final product in which R_1 contains or optionally contains a halogenated phenyl group." Anslyn Report ¶ 46. In my opinion, the first German priority application adequately discloses to one of skill in the art the halogenated phenyl alkyl R_1 derivatives to meet the written description requirement of the U.S. patent law.

D. PERSON OF ORDINARY SKILL IN THE ART

17. I understand that patent claims must be construed, and the specification of a patent read, as a person of ordinary skill in the art would have understood them at the time of the filing of the patent.

18. In my opinion, a person of ordinary skill in this art at the time of the invention would have been an individual with an advanced degree (M.S. or Ph.D.) in organic chemistry or pharmacology and having two or three years of laboratory experience in medicinal chemistry in an academic or industry setting. A person without a graduate degree, but having more laboratory

experience in this field, could also be considered a person of ordinary skill at the time of the invention.[1]

E. UNDERSTANDING OF RELEVANT PATENT LAW REQUIREMENTS

19. I understand that when a patent is issued after examination by the U.S. Patent and Trademark Office, the patent is presumed to be valid. This presumption can only be overcome by clear and convincing evidence of facts to the contrary. I further understand that "clear and convincing evidence" is a much higher standard than a suggestion or a presumption or one possible interpretation out of many; it is evidence that produces in one's mind a firm belief or conviction that the allegations sought to be proved by the evidence are true.

20. I understand that Section 112 of the patent law provides that the "specification shall contain a written description of the invention...." It is my further understanding that the subject matter of a later filed claim does not need to be described literally or *in haec verba* in an earlier filed priority application in order for the description requirement to be satisfied. I have been advised that the appearance of a claim element that is not expressly delineated in the specification of a patent does not violate the written description requirement if the specification makes it clear to one skilled in the art that the claim element has been invented. Thus, a priority application provides sufficient description of an invention if, taken as a whole, it reasonably conveys to those skilled in the art that the inventors were in possession of the subject matter they later claim.

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[1] I note that Barr Laboratories' expert Dr. Anslyn suggests that the skilled artisan has a lower level of training and less experience in the field of drug discovery. While I believe his definition underestimates the capabilities of one of ordinary skill, I note that the opinions I offer in this report would not change in the event that Barr's definition is accepted by the Court.

21. It is also my understanding that a parent application satisfies the written description requirement if it provides adequate direction to those skilled in the art that reasonably leads them to the claimed compounds, in other words, that an adequate description of a process for synthesizing a compound may be considered an adequate description of the compound itself.

22. In this case, I understand that in order to constitute prior invention by another in this country who had not abandoned, suppressed, or concealed it under Section 102(g) of the patent law, Barr must show both conception and reduction to practice of the alleged invention. I also understand that to achieve actual reduction to practice, an inventor must not only construct an embodiment of the invention but must also test the product or process so as to establish its capacity to perform the intended purpose successfully. In the context of a new chemical compound or composition, I understand that utility of the new chemical compound or composition must be established by testing and that the inventor must recognize and appreciate that the tests were successful. In other words, there is no invention until the alleged inventor interprets or evaluates the results and understands them to demonstrate the invention. I thus understand that prior invention cannot be established without evidence for this timely testing, evaluation, and demonstration of the invention.

F. TUTORIAL ON DRUG DISCOVERY

23. The discovery of a new pharmaceutical agent begins with the consideration of a disease area, such as cancer, heart disease, diabetes, a neurological disorder, etc. In some cases, a researcher may be able to focus his attention on a specific biological mechanism of action, often referred to as a *target*, that is known to play a role in the disease. In particularly favorable circumstances, it may be possible to probe the function of the biological target in a simple *in*

vitro system (i.e., in a test tube – or the modern equivalent), which facilitates the evaluation of drug candidates that may show promise in treating the disease.

24. However, in other cases, a specific biological target for treating the disease may not have been identified, in which case a researcher must rely on animal testing (*i.e.*, an *in vivo* model) to evaluate the promise of potential lead compounds phenomenologically. The researcher may thus be able to identify the biological target only after compounds effective in modulating the disease have been found and their mechanism of action elucidated. Even in instances in which a target may have been identified biologically, the complexity of the system in which it functions may be such that the effect of increasing or decreasing its activity cannot be evaluated in a simple *in vitro* experiment. Indeed, the complexity of every biological system is such that any drug must be evaluated in extensive animal and, eventually, human clinical trials before its efficacy and potential toxicity can be fully understood.

25. From the standpoint of a medicinal chemist, the starting point in the search for a new drug is a "lead compound," a molecule that shows some of the desired biological activity. There are a number of ways in which such starting points can be identified. One strategy is to screen collections of compounds, such as those archived from past pharmaceutical research or being synthesized in other programs, or collections of extracts from natural sources. While not completely random, the screening approach is very much like searching for the needle in the haystack, since the likelihood of finding a useful lead is very small. This method is also impractical unless the screen is a very straightforward *in vitro* test.

26. Another approach to the identification of a lead compound is to build on what is known in the art by considering what compounds have been described in the scientific literature or in patents as showing the desired activity. There are often many such avenues to consider,

based on what others have reported or claimed, and the task is to select a starting point that appears to offer the most promise. One skilled in the art may consider a number of characteristics in selecting a starting compound, such as the potency of its effect on the desired target, or its selectivity for the desired target as opposed to an undesired target, or the least toxicity, or the most favorable pharmacodynamic profile. He also considers what may be known about *structure-activity relationships* or *SAR*; that is, what has been reported in the prior art regarding the effect of structural differences on a particular biological property (I address this issue in greater detail below). Information from the prior art is important, since it may direct one skilled in the art toward particularly promising molecular structures or scaffolds, and may teach away from structural features that result in unfavorable properties.

27. It is extremely unlikely that a medicinal chemist is able to identify a lead compound, either from screening or from the prior art, that has all the properties required of a new drug. Invariably, modifications to the structure are undertaken to change the properties so that it has the desired potency and selectivity for the biological target, so that it has an acceptably low toxicity when tested in animals, so that it can be adequately absorbed from its site of administration (optimally by oral dosage), and so that it is distributed throughout the body and not metabolized or excreted too slowly or too quickly.

28. These requirements are addressed in a hierarchical approach: typically, the medicinal chemist first tries to improve the potency of the lead compounds against the desired target. He then looks for compounds that do not hit related or undesired targets, while trying to preserve the primary activity. Potent and selective compounds are evaluated for toxicity, and modifications are made to try to identify non-toxic compounds that are still potent and selective. Compounds that are potent, selective, and that appear to be reasonably safe may not be well-

absorbed, they may be rapidly metabolized, or the mechanism by which they are excreted from the body may be such that they are cleared rapidly from the bloodstream or, conversely, may persist too long and build up over time. In the development of compounds that must act in the central nervous system, the "blood-brain barrier" is another hurdle that the drug must cross. Similarly, in the development of compounds that act in the peripheral nervous system, compounds that also elicit central behavioral effects may not be suitable as drugs. While there is some temporal overlap in the sequence in which these properties of a drug candidate are addressed, it is clear that the problem faced by the medicinal chemist involves balancing many independent variables, all of which are important and difficult to predict.

Structure-Activity Relationships (SAR)

29. It is the nature of scientists to discern patterns from their data and to attempt to extrapolate from their experience in designing further experiments. In the search for novel and improved drugs, this conceptual approach is embodied in what has become known as "structure-activity relationships" or "SAR." In an SAR analysis, a medicinal chemist looks for a trend in a property of interest, for example, a biological effect in an *in vitro* or *in vivo* model system, as the structures of the molecules are modified. To appreciate the role of SAR analysis, it helps to understand what insights or intuition a medicinal chemist gains from observing the effects that changes in molecular structure have on the biological or other properties of a lead compound; in particular, it is important to understand their limitations. To the extent a researcher tries to glean from SAR analyses some indication of which compounds to make and which compounds to avoid, hypotheses of this sort may be of potential use in guiding his decision. However, such hypotheses are by definition derived from a retrospective analysis, and their utility is critically

dependent on the type of data from which they are derived and on the nature of the extrapolation that the researcher makes in applying them to an unknown structure.

30. As an example of a typical SAR hypothesis, if a researcher observes that replacement of a particular hydrogen atom with a hydroxyl group (OH) leads to an improvement in certain activity between one pair of molecules, he might hope to see a similar difference in that activity if the same substitution is made in a closely related pair of molecules. For there to be any validity to this inference, all other elements of the experiment must be the same; *i.e.*, the activity must be measured under similar conditions and against the same target. As one would expect, the more that the comparison compounds differ from each other, the less confidence the researcher can have in his hypothesis.

31. An SAR hypothesis derived from one kind of data provides no insight into properties that depend on different types of data. For example, if one just determines the *in vitro* activity of two related compounds, one containing a hydroxyl substituent and the other a hydrogen, this information is not useful for inferring what the difference between the compounds would be in terms of other *in vitro* activity or their absorption, tissue distribution, metabolism, excretion, toxicity - in short, their efficacy as drugs *in vivo*.

32. It is intuitively apparent why one can have little confidence in the generality of an SAR analysis derived from a multivariate system. For instance, if the biological test involves an *in vivo* animal model system that depends on a CNS effect, the molecular interaction between the lead compound and the biological target will be only one factor out of many in determining the observed activity. For one series of compounds, the limiting factor may be the potency of this interaction, whereas for another series, penetration of the blood-brain barrier may restrict the observed effect. Since these various biological properties are not affected by structural

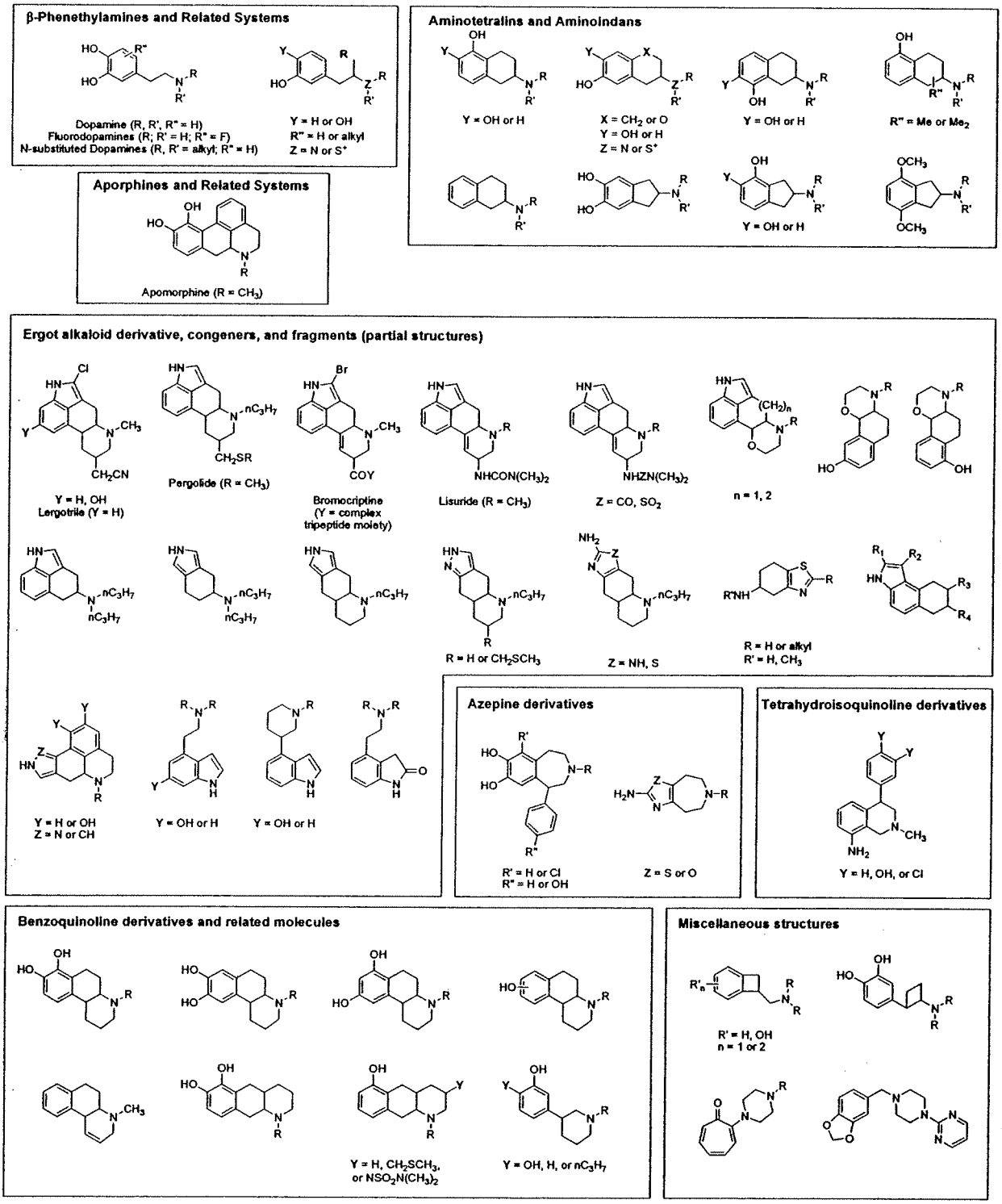
alterations in the same way, the SAR observed for one series of compounds may be completely irrelevant for another.

Advancement of a Lead Compound to a Clinical Candidate

33. As noted above, there is far more involved in the invention of a drug than simply obtaining a compound that manifests activity against a particular biological target. One cannot file a New Drug Application with the Food and Drug Administration for approval to market a drug simply on the strength of the observation that "this molecule showed potent dopaminergic activity in the rat." Nor can one even submit an Investigational New Drug application for permission to administer the compound to humans in a clinical trial at this point. A clinical candidate must satisfy a multitude of biological, pharmacological, and physicochemical characteristics before it reaches this stage of human testing or commercial use. All of these characteristics depend on the molecular structure, none of them can be predicted with any degree of confidence, and they can be obtained only through extensive experimentation.

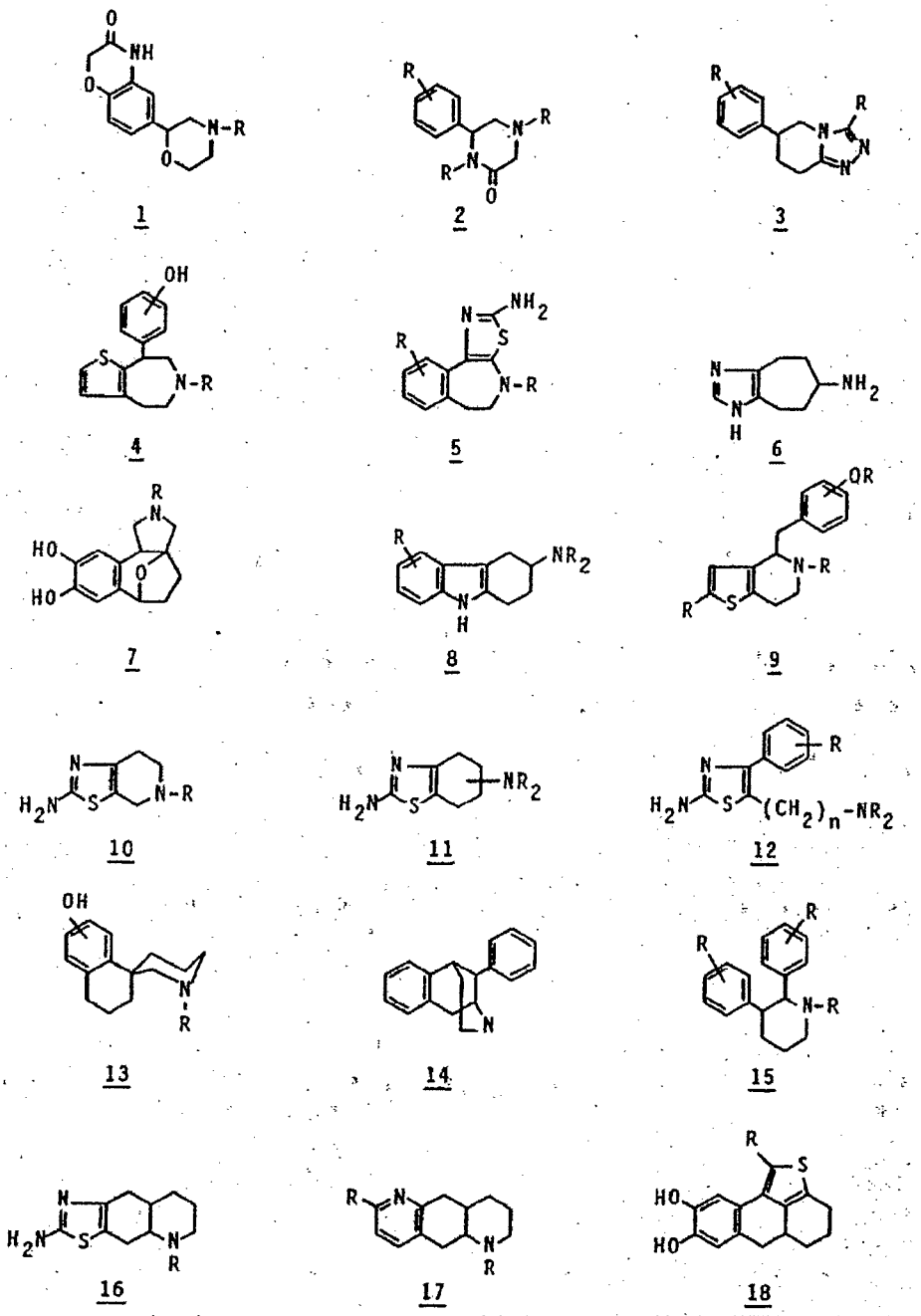
G. BOEHRINGER INVENTORS' WORK

34. To put into context the invention of pramipexole, I outline the state of the art in the field of dopamine agonists as of that time. An enormous number of chemical structures were known to have dopaminergic activity, as shown in the chart below, which was derived from a comprehensive review article published in 1985 (J. G. Cannon, *Prog. Drug. Res.* **1985**, *29*, 303-414 "Dopamine agonists: Structure-activity relationships"):



35. In addition to the enormous diversity of structures from the prior art, Dr. Claus Schneider, one of the inventors of the '812 Patent and a medicinal chemist working at

Boehringer's Ingelheim research facility, and his colleagues considered and investigated many other structural classes that were not known from the prior art to have dopaminergic activity. Dr. Schneider's "Tätigkeitsbericht IV/1984" records the following ring systems as "Bearbeitete Strukturklassen bei der Suche von Dopaminagonisten" (Structural classes worked on in the search for dopamine agonists) (Exh. 40 at BOE00849215):



36. The Cannon 1985 review of the prior art, as well as Dr. Schneider's 1984 report of his efforts, show that the 2,6-diamino-4,5,6,7-tetrahydrobenzthiazole framework was not a clear-cut starting point in a search for compounds with dopaminergic agonist activity. However, from the broad search that Dr. Schneider's lab undertook, testing revealed promising activity for some derivatives in this class, in particular the 6-monopropylamino compound, prompting the further investigation of this chemical series that ultimately led to the selection of pramipexole as a candidate for development of an anti-Parkinson's agent.

37. Dr. Schneider began his investigation of diaminotetrahydrobenzthiazoles in late 1983 as part of his effort to find compounds that could be useful in the treatment of schizophrenia. *See* Schneider Dep. 25:4-5; 45:3-22. In this June 1984 quarterly activity report, Dr. Schneider recorded the synthesis and physical characterization (by melting point) of some 11 diaminotetrahydrobenzthiazoles with different amino substituents at the 2- and 5- or 6-positions. Exh. 9, BOE00849177-78.

38. In his September 1984 quarterly activity report, Dr. Schneider indicated that in the intervening reporting period, his lab had synthesized two aminotetrahydrobenzthiazole derivatives that he considered "wichtigen Varianten" (important variants), which were identified by the codes "SND 919" and "SND 920." Exh. 35, BOE00849198. SND 919 was the Boehringer designation for the 2-amino-6-propylamino derivative and SND 920 was the 2-amino-6-dipropylamino derivative. Dr. Schneider noted that the initial biological evaluation of these compounds showed an interesting profile. In particular, he reported that SND 919 exhibited presynaptic dopaminergic activity, as manifested by pronounced inhibition of the synthesis of DOPA; moreover, this compound appeared to have favorable tolerance in animal experiments. *Id.* at BOE 00849199.

39. After his internal report of the synthesis and initial testing of some diaminotetrahydrobenzthiazoles, Dr. Schneider learned that Drs. Gerhart Griss and Rudolf Hurnaus, scientists at Boehringer's Biberach research facility, had independently synthesized and tested some compounds from this chemical series. *See* Schneider Dep. 34:25-35:22; 93:25-94:21. After consultation between Dr. Schneider and Dr. Hurnaus (Dr. Griss died in 1983), it was decided that continued research on diaminotetrahydrobenzthiazoles would be the responsibility of Dr. Schneider's laboratory. *See* Hurnaus Dep. 49:1-52:8.

40. In his December 1984 quarterly activity report, Dr. Schneider reported that during 1984, his lab had synthesized 200 compounds from 18 different structure classes in their search for antipsychotics/dopamine agonists; compounds from three classes had thus far demonstrated activity as inhibitors of dopamine synthesis. Increased dopamine synthesis, which still needed to be verified, was observed in a fourth class. Exh. 40 at BOE00849214. He also reported that the emphasis of his laboratory during the quarter was on the continued synthesis of diaminotetrahydrobenzthiazoles and that additional compounds within the class had been prepared using the newly developed synthesis routes. *Id.* By that time, his lab was concentrating on the 6-monoalkylamino derivatives because they had found that 6-dialkylamino derivatives were not as well tolerated. *Id.* at BOE00849216. Dr. Schneider singled out SND 919 as a diaminotetrahydrobenzthiazole that was being investigated more broadly, reflecting the encouraging results emerging from biological testing of this compound. *Id.* at BOE00849217. He further noted that work on the diaminotetrahydrobenzthiazoles had, for the time being, largely been wound down, with attention directed toward a different ring system, the diaminothiazolocyclopentanes. *Id.*

41. In his March 1985 quarterly activity report, Dr. Schneider characterized SND 919 as an "Entwicklungssubstanz" (development substance), meaning that it had been approved for further investigation in anticipation of carrying it forward into preclinical development. *See* Schneider Dep. 121:10-122:8; Exh. 41 at BOE00849166. Dr. Schneider reported that the potential neuroleptic and anti-Parkinsonian properties of SND 919 were better than those of other compounds due to reduced adrenergic effects combined with the highest activity so far measured as an inhibitor of dopamine synthesis. Exh. 41 at BOE00849166. In addition, SND 919 appeared to improve the symptoms of MPTP monkeys (those with induced symptoms akin to Parkinson's disease) for a distinctly longer period of time. *Id.* As a consequence of the focus on SND 919, the emphasis of his laboratory work for the quarter was to develop a manufacturing protocol for SND 919 and prepare 30 g of this compound for additional testing. *Id.*

42. In his May 1985 quarterly activity report, Dr. Schneider described a new synthetic route for SND 919 that was superior to those employed previously. Exh. 42 at BOE00849180. He also described in more detail the method for preparing the individual enantiomers of SND 919, designated SND 919 Y (–) and SND 919 X (+). The individual enantiomers and the racemic form were compared with respect to their biological activity and Boehringer determined that the (–)-enantiomer ("SND CL 2 Y (–)") had the highest activity as a dopaminergic agent. *Id.* at BOE00849182-83. Finally, Dr. Schneider provided a retrospective overview of the structure-activity relationships for a dozen of the variously substituted 2,6-diaminotetrahydrobenzthiazoles that had been investigated. *Id.* at BOE00849187.

43. On June 14, 1985, Boehringer decided to pursue development of the more active SND 919 Y enantiomer. *See* BOE00132270-71. Preliminary pharmacological and biochemical tests showed SND 919 CL 2 Y (pramipexole) to be more effective than the racemate, and that the

X form is substantially weaker. *Id.* Boehringer also reported internally that the Y enantiomer and the racemate did not differ in the preliminary acute toxicity tests in the mouse. *Id.* In his October 1985 quarterly activity report, Dr. Schneider reported that, because SND 919 Y had been selected for further development, his lab had concentrated their activities during the report period on developing a procedure for the kilogram-scale preparation of SND 919 CL 2 Y. Exh. 50 at BOE00849205. The report also recorded additional biological test results for the enantiomers of SND 919 and the racemate, which confirmed that the Y enantiomer was the best candidate for development as a dopaminergic agent. *Id.* at BOE00849209.

44. Between July and September 1985, various pharmacological tests were carried out to compare SND 919 (racemate) with B-HT 920 and BX-OX 280, the other compounds that were under investigation in Boehringer's search for dopamine autoreceptor agonists. *See* BOE00004167-77. In a pharmacological model for Parkinson's disease, SND 919 proved to be equivalent or superior to the comparison compounds in their action on the hypersensitive postsynaptic dopamine receptors, and definitely superior with regard to the duration of this effect. *Id.* at BOE00004172. The results led the Boehringer investigators to designate SND 919 as the leader and most favorable among the three comparison compounds because it showed most favorable ratio of desired dopamine activity to undesired α-adreno receptor activity. *Id.* Further pharmacological tests continued to show that SND 919 CL 2 Y was superior to the SND 919 racemate and other potential dopaminergic compounds that had been selected for further testing. *See* BOE00004178-97.

45. By August 1988, numerous biological tests with SND 919 CL 2 Y (pramipexole) had been carried out, leading to the conclusion that SND 919 CL 2 Y "shares many of the characteristics of B-HT 920 but is much less active on α2 receptors so that [it is expected to

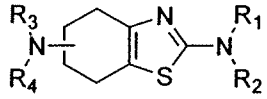
have] less pronounced effects on the cardiovascular system and lower incidence of nausea and vomiting and perhaps sedation." *See* BOE00037825-61 at BOE00037828. In particular, in studies in animals whose dopaminergic system had been damaged irreversibly using MPTP, SND 919 CL 2 Y was shown to antagonize motor deficit and other Parkinson-like symptoms, including tremor, dyskinesia and dorsi-flexion, in a dose-dependent way. *Id.* at BOE00037833. Notably, SND 919 CL 2 Y, in contrast to B-HT 920, did not produce sedation. *Id.* at BOE00037834. Moreover, in both *in vitro* and *in vivo* pharmacological tests, pramipexole was shown to be a highly potent, presynaptic dopamine receptor agonist with a marked inhibitory effect both on the rate of dopamine synthesis and on dopamine release. *Id.* at BOE00037835-36.

46. Pramipexole eventually was tested on humans in Phase III clinical trials. Those trials showed that as initial therapy in early Parkinson's disease, pramipexole (1) significantly reduces the risk of developing dyskinesias; (2) enhances patient functioning; and (3) may slow the loss of dopaminergic neurons. The clinical trials also demonstrated that as adjunct therapy in advanced Parkinson's disease, pramipexole (1) reduces tremor; (2) reduces the daily levodopa dosage without deterioration of motor response; (3) increase "on" time and decreases "off" time; and (4) enhances patient functioning. *See* BOE00754889-929 at BOE00754899. Based upon such trials, pramipexole was commercialized as Mirapex® in the United States. The United States Food and Drug Administration approved various dosage strengths of Mirapex® for the treatment of the signs and symptoms of idiopathic Parkinson's disease on July 1, 1997. *See* July 1, 1997 FDA Approval Letter; BOE00116352.

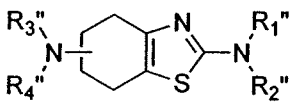
H. THE GERMAN PRIORITY APPLICATIONS

47. The German patent applications DE 3 447 075 filed December 22, 1984 ("the German '075 application") and DE 3 508 947 filed March 13, 1985 ("the German '947

application") were cited as priority disclosures in the U.S. application that matured into the '812 Patent. The German '075 application defines and claims a genus of compounds described as follows (Exh. 53 at BARR028314):

> Tetrahydro-benzthiazoles of general formula
>
>  (I)
>
> wherein
>
> R_1 represents a hydrogen atom, an alkyl group having 1 to 6 carbon atoms, an alkenyl or alkynyl group each having 3 to 6 carbon atoms, an alkanoyl group having 1 to 6 carbon atoms, a phenyl alkyl group or phenyl alkanoyl group having 1 to 3 carbon atoms in the alkyl part,
>
> R_2 represents a hydrogen atom or an alkyl group with 1 to 4 carbon atoms,
>
> R_3 represents a hydrogen atom, an alkyl group with 1 to 7 carbon atoms, a cycloalkyl group having 3 to 7 carbon atoms, an alkenyl or alkynyl group having 3 to 6 carbon atoms, an alkanoyl group having 1 to 7 carbon atoms, a phenyl alkyl group or phenyl alkanoyl group having 1 to 3 carbon atoms in the alkyl part, whilst the phenyl nucleus may be substituted by fluorine, chlorine, or bromine atoms,
>
> R_4 represents a hydrogen atom, an alkyl group with 1 to 4 carbon atoms, an alkenyl or alkynyl group having 3 to 6 carbon atoms or
>
> R_3 and R_4 together with the nitrogen atom between them represent a pyrrolidino, piperidino, hexamethyleneimino or morpholino group, [] and the acid addition salts thereof.

48. The German '075 application discloses several conventional methods for preparing the compounds described in the application. One, designated as method "d)", involves reduction of an acyl or phenylacyl derivative; this method is illustrated by Examples 8 and 10 of the German priority applications:

> d) In order to prepare compounds of general formula I wherein at least one of the groups R_1, R_2, R_3 or R_4 represents one of the above-mentioned alkyl, cycloalkyl, alkenyl or phenylalkyl groups:
>
> Reduction of a compound of general formula
>
>  VII

wherein

at least one of the acyl groups R_1", R_2", R_3" or R_4" represents one of the acyl or phenylacyl groups mentioned hereinbefore and the other groups have the meanings given for R_1, R_2, R_3 and R_4 hereinbefore, with a metal hydride in a solvent.

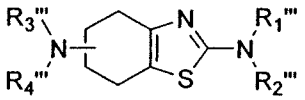
[Additional details regarding suitable solvents, advantageous reagents, and conditions for the reduction reaction are given.]

(Exh. 53 at BARR028277-78.)

49. Another method disclosed, method "e)", describes the introduction of nitrogen substituents by alkylation and acylation; method "e)" is illustrated by Examples 5, 6, 7, 9, and 12 of the German priority applications:

e) In order to prepare compounds of general formula I wherein at least one of the groups R_1, R_2, R_3 or R_4 represents one of the above-mentioned alkyl, cycloalkyl, alkenyl, alkynyl or phenylalkyl groups mentioned hereinbefore:

Reacting a compound of general formula



(VIII)

wherein

at least one of the groups R_1'''', R_2'''', R_3'''' or R_4'''' represents a hydrogen atom and the other groups R_1'''', R_2'''', R_3'''' or R_4'''' have the meanings given for R_1 to R_4 hereinbefore, with a compound of general formula

$R_5 - Z$ (IX)

wherein

R_5 represents one of the alkyl, cycloalkyl, alkenyl, alkynyl or phenylalkyl groups mentioned for R_1 to R_4 hereinbefore and Z represents a nucleophilically exchangeable group such as a halogen atom or a sulfonic acid, e.g., a chlorine, bromine or iodine atom, methoxysulfonyloxy or p-toluenesulfonyloxy group, or Z together with an adjacent hydrogen of the group R_5 represents an oxygen.

[Additional details regarding suitable solvents, advantageous reagents, and conditions for the alkylation reaction are given.]

If according to the invention a compound of general formula I is obtained wherein at least one of the groups R_1, R_2, R_3 or R_4 represents a hydrogen atom, this may be converted by corresponding acylation into a

corresponding compound of general formula I wherein at least one of the groups R_1, R_2, R_3 or R_4 represents one of the acyl groups mentioned hereinbefore.

[Additional details regarding suitable solvents, advantageous reagents, and conditions for the acylation reaction are given.]

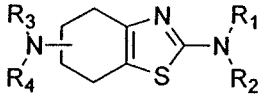
(Exh. 53 at BARR028278-80.)

50. These methods involve very general synthetic reactions that were well known in the art of organic synthesis. One of ordinary skill would understand that, either singly or in combination, they enable the preparation of a vast range of substituted diamino-4,5,6,7-tetra-hydrobenzthiazoles.

I. THE '812 PATENT

51. The '812 Patent defines and claims a genus of compounds similar to those of the German '075 application:

A tetrahydro-benzthiazole of the formula:



(I)

wherein

R_1 is a hydrogen atom, an alkyl group having 1 to 6 carbon atoms, an alkenyl or alkynyl group each having 3 to 6 carbon atoms, an alkanoyl group having 1 o 6 carbon atoms, a phenyl alkyl group or phenyl alkanoyl group having 1 to 3 carbon atoms in the alkyl part, wherein the above mentioned phenyl nuclei may be substituted by 1 or 2 halogen atoms;

R_2 is a hydrogen atom or an alkyl group with 1 to 4 carbon atoms;

R_3 is a hydrogen atom, an alkyl group with 1 to 7 carbon atoms, a cycloalkyl group having 3 to 7 carbon atoms, an alkenyl or alkynyl group having 3 to 6 carbon atoms, an alkanoyl group having 1 to 7 carbon atoms, a phenyl alkyl group or phenyl alkanoyl group having 1 to 3 carbon atoms in the alkyl part, whilst the phenyl nucleus may be substituted by fluorine, chlorine, or bromine atoms; and,

R_4 is a hydrogen atom, an alkyl group with 1 to 4 carbon atoms, an alkenyl or alkynyl group having 3 to 6 carbon atoms; or,

R_3 and R_4 together with the nitrogen atom between them form a piperidino, hexamethyleneimino or morpholino group; or, an acid addition salt thereof.

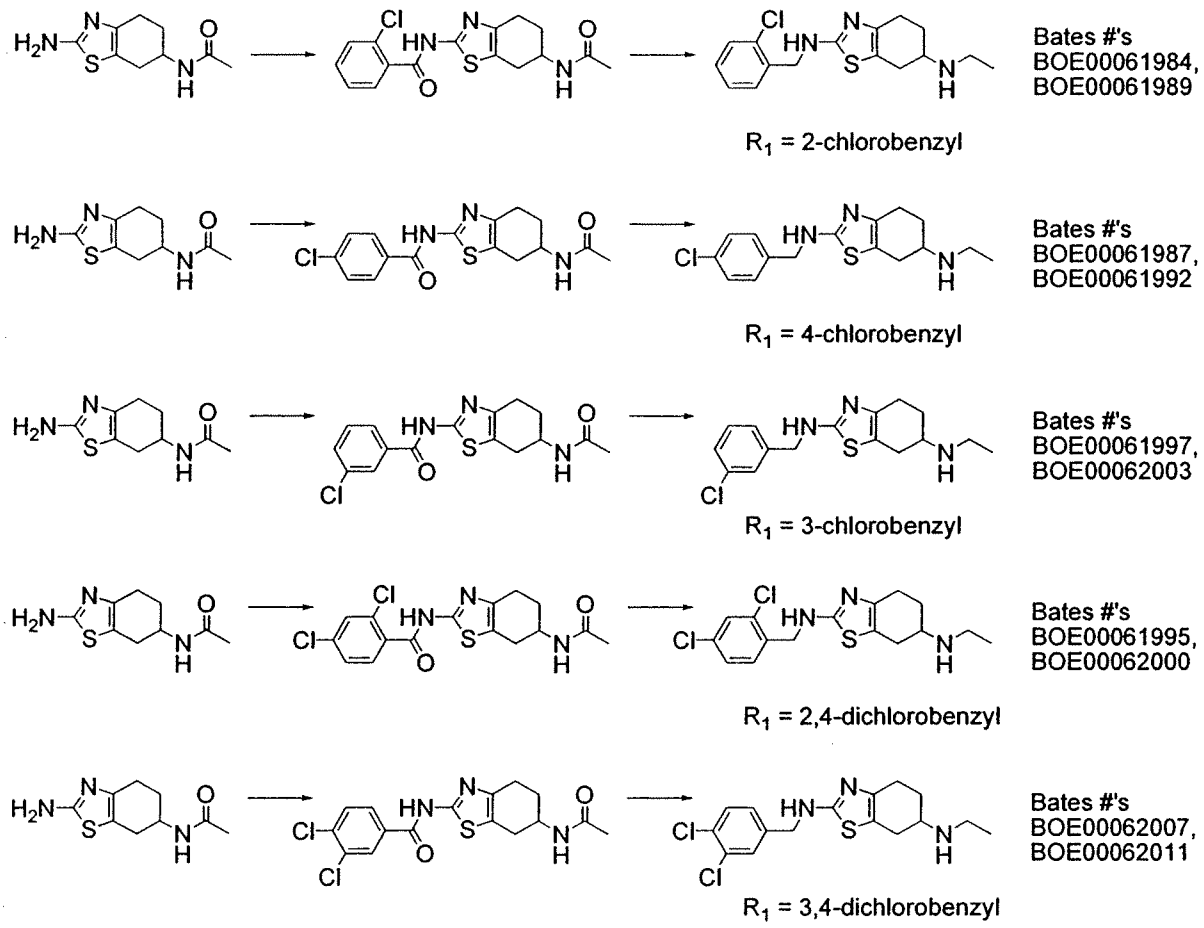
(Exh. 3, BOE00000014.)

52. The only difference with respect to phenyl substitution between the genus of Claim 1 of the '812 Patent and that of Claim 1 of the German '075 application is the explicit inclusion of halogen substituents on the phenyl alkyl and phenyl alkanoyl groups within the definitions of both R_1 and R_3; such substituents are only enumerated explicitly for R_3 in the genus of Claim 1 of the German '075 application.

53. The '812 Patent discloses the identical synthetic methods for preparation of the compounds of the invention as described in the earlier German applications, and includes all of the specific examples those documents disclosed. Also included within Example 10 of the '812 Patent are three compounds with chlorinated benzyl substituents on the 2-amino group, as examples in which R_1 is a halogenated phenyl alkyl group. Exh. 3, BOE00000012, column 20, lines 23-44.

J. THE INVENTORS' SYNTHESES OF HALOGENATED PHENYLALKYL DERIVATIVES

54. I have reviewed the laboratory notebooks of Michael Lavall, a technical assistant in Dr. Schneider's laboratory, and I note that syntheses of a number of diaminotetrahydrobenzthiazoles with chlorinated benzyl groups as R_1 substituents are recorded therein. These syntheses, which were carried out in January 1985, are illustrated below:



K. THE OPINIONS OFFERED BY DR. ANSLYN

55. Barr's expert, Dr. Anslyn, notes the expanded definition for the R_1 groups in Claim 1 of the '812 Patent, as well as the inclusion of chlorinated phenyl alkyl groups as R_1 groups in the enumerated examples of the R_1R_2N fragment (column 2 of the Patent), in the description of particularly preferred compounds (column 3), and within Example 10. *See* Anslyn Report, ¶¶ 40-44.

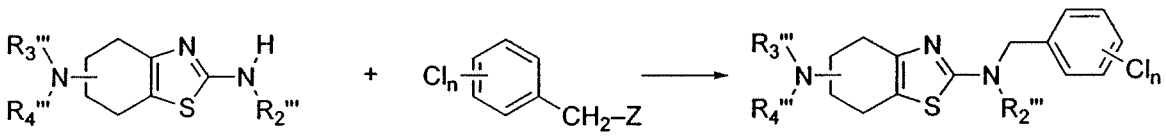
56. In Dr. Anslyn's opinion, "there is nothing in either of the German applications that discloses implicitly or explicitly to the skilled artisan, any starting material, intermediate, or final product in which R_1 contains or optionally contains a halogenated phenyl group." *Id.* at ¶ 46.

L. THE TEACHINGS OF THE GERMAN PRIORITY APPLICATIONS

57. In light of my understanding of the legal requirements of 35 U.S.C. Section 112, as summarized above, I disagree with Dr. Anslyn's opinion set forth in the previous paragraph. One of ordinary skill in the art of organic chemistry would have understood that the methods used to introduce halogenated phenylalkyl substituents, such as the 2-chlorobenzyl, 4-chlorobenzyl, or 3,4-dichlorobenzyl groups, are the same as those used to introduce unsubstituted benzyl or other phenylalkyl substituents into a molecule. Thus, inherently, the synthetic routes disclosed in the German priority applications would reasonably enable one of ordinary skill to make diaminotetrahydrobenzthiazoles with halogenated benzyl or other phenylalkyl groups as R_1 substituents.

58. I note also that neither method "d)" nor method "e)" of the German priority applications distinguish the R_1 and R_2 substituents on the 2-amino group from the R_3 and R_4 substituents on the amino group of the 6-membered ring. *See* Exh. 53, BARR028277-80. That is, the German priority applications describe identical reactions for introducing these substituents. One of ordinary skill in the art would have known that these reactions enable the introduction of a halogenated phenylalkyl or phenylalkanoyl groups as either R_1 or R_3 substituents as straightforwardly as they would the non-halogenated groups.

59. The generality of this chemistry, and the ease with which one of ordinary skill could apply it to the synthesis of halogenated R_1 groups, is further illustrated by the following sequence, which falls squarely within the boundaries of method "e)" of the German priority applications:

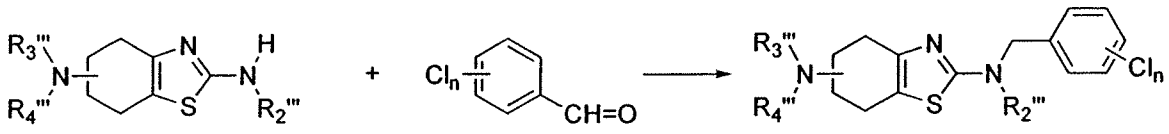


("a compound of general formula VIII wherein at least one of the groups R_1''', R_2''', R_3''' or R_4''' represents a hydrogen atom ...")

("R_5 represents one of the ... phenylalkyl groups mentioned for R_1 to R_4 hereinbefore...")

60. The definition for R_5 includes all of the phenylalkyl group variations disclosed for R_1 to R_4 "hereinbefore". *See Id.* at BARR028279. Because the description of the R_3 group in the specification includes those "having 1 to 3 carbon atoms in the alkyl part, whilst the phenyl nucleus may be substituted by fluorine, chlorine, or bromine atoms," one of skill in the art would have understood the definition of R_5 to include halogenated phenylalkyl and phenylalkanoyl groups. Thus, method "e)" clearly embraces the synthesis of diaminotetrahydrobenzthiazoles with halogenated phenylalkyl and phenylalkanoyl groups at the R_1 position.

61. The variation of method "e)" in which the R substituents are introduced by reductive amination instead of alkylation is similarly applicable to the synthesis of diaminotetrahydrobenzthiazoles with halogenated phenylalkyl and phenylalkanoyl groups at the R_1 position:



("... or Z together with an adjacent hydrogen of the group R_5 represents an oxygen.")

62. I note that method "d)" may also be employed for the preparation of diaminotetra-hydrobenzthiazoles with halogenated phenylalkyl substituents at the R_1 position:

("a compound of general formula VII wherein at least one of the groups R_1", R_2", R_3" or R_4" represents one of the ... phenylacyl groups mentioned hereinbefore")

63. The definition of "the phenylacyl groups mentioned hereinbefore" in compounds of general formula VII encompasses those defined for both R_1 and R_3 and thus includes groups in which the phenyl nucleus may be substituted by fluorine, chlorine, or bromine atoms. *See Id.* at BARR028278.

64. As I noted above, these interpretations are fully in accord with what one of ordinary skill in organic chemistry would understand are possible synthetic methods. Indeed, the applicability of method "d)" to the synthesis of derivatives containing a chlorobenzyl or dichlorobenzyl group as the R_1 substituent is confirmed by the fact that Dr. Schneider's assistant Michael Lavall used the method to prepare five such analogs. I also note that the compounds of Example 10 of the '812 Patent that contain chlorinated benzyl groups as the R_1 substituent were prepared by method "d)."

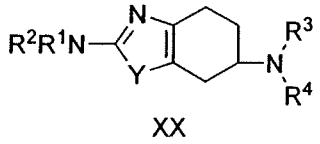
65. Furthermore, a clear reading of the synthetic methods disclosed in the German priority applications contradicts Dr. Anslyn's statement that these documents do not disclose "any starting material, intermediate, or final product in which R_1 contains or optionally contains a halogenated phenyl group." Anslyn Report ¶¶ 18, 46. The definition of a compound of general formula VII in method "d)" includes all phenylacyl groups, halogenated or non-halogenated, within the definition of R_1". *See Id.* at BARR028277-78. Compound VII would be considered by one of ordinary skill as either a starting material or intermediate.

66. Similarly, the definition of the R_5 group in formula IX, which would be considered a starting material in method "e)," encompasses all the variations "mentioned for R_1 to R_4 hereinbefore"; this definition includes the halogenated phenylalkyl groups of the R_3 moiety. *Id.* at BARR028279.

M. RESEARCH WORK BY LILLY SCIENTISTS

67. It is my understanding that Barr, and only Barr, alleges that the work by Lilly scientists, Dr. Bennett Laguzza and Mr. William Turner, constitutes prior invention of diaminotetrahydro-benzthiazole dopaminergic agents under Section 102(g). Neither the purported inventors nor Lilly has made such an assertion or otherwise endorsed Barr's position.

68. Lilly's patent application Ser. No. 747,748 informs one skilled in the art that the compounds that Dr. Laguzza and Mr. Turner believed to have invented were tetrahydrobenzthiazoles (Y = S) and -benzoxazoles (Y = O) of formula XX:



XX

> wherein Y is S or O, R^1 and R^2 are independently H, methyl, ethyl, or n-propyl, and R^3 and R^4 are independently H, methyl, ethyl, n-propyl or allyl; and pharmaceutically-acceptable acid addition salts thereof formed with non-toxic acids.

Exh. 18, BARR027394.

69. The specification of this application makes it clear that the only compounds predicted to have dopamine agonist activity are those in which the nitrogen on the 6-membered ring is disubstituted (that is, both R^3 and R^4 are alkyl or allyl groups):

> The compounds of this invention wherein neither R^3 nor R^4 is H have receptor agonist activity; i.e., they can increase the amounts centrally or peripherally or both of certain neurohormones.

Id.

70. Although compounds in which the nitrogen on the 6-membered ring is monosubstituted are claimed in this application, the specification makes it clear that they were understood to have utility only as intermediates for the synthesis of the active disubstituted derivatives:

> Compounds according to XX wherein one or both of R^3 and R^4 is H are intermediates in that they can be allylated or alkylated to yield compounds of this invention wherein R^3 and R^4 are individually methyl, ethyl, n-propyl or allyl.

Id.

71. It is clear that the Lilly scientists did not expect diaminotetrahydrobenzthiazoles with a monoalkylamino substituent at the 6- position to have receptor agonist activity. This conclusion is not only supported by the explicit teaching of their patent application, but also by the fact that they never even made such a compound to test for activity. I understand that Mr. Turner testified that he had never synthesized a compound that fit that description or even thought about doing so. *See* Turner Dep 89:17-91:2. I also understand that there is no evidence that Dr. Laguzza ever made such a compound either.

72. I note that Dr. Anslyn in his report does not address any issue relating to obviousness for any claims of the '812 Patent. Although he addresses the structural relationship between the 6-dialkylamino compounds synthesized by the Lilly scientists and the compounds encompassed by claims 1-6 and dependent claim 8 of the '812 Patent, he specifically excludes claims 7, 9, and 10 from his discussion. Claims 7, 9 and 10 of the '812 Patent are directed to 6-monoalkylamino derivatives, which were never synthesized by the Lilly scientists and which they did not expect to have receptor agonist activity.

73. Dr. Anslyn offers no opinion whether the compounds encompassed by claims 7, 9 and 10 of the '812 Patent would have been obvious to one skilled in the art, nor does he cite any

factual support for such an opinion, were it to be found that the three dialkylaminotetrahydro-benzthiazole compounds that the Lilly scientists synthesized were to constitute a prior invention. Of course, the fact that the Lilly scientists' own patent application taught that the monoalkyl derivatives, like those in claims 7, 9 and 10 of the '812 Patent, would not be useful as receptor agonists leads to the opposite conclusion – that is, that the dopaminergic activity of monoalkyl derivatives, such as pramipexole, was unexpected and nonobvious.

2-Amino-6-di-n-propylamino-4,5,6,7-tetrahydrobenzthiazole (Lilly Compound 188305)

74. In light of the legal requirements for an invention to be considered "reduced to practice", I see no evidence from the documents or deposition testimony from Lilly scientists that Dr. Laguzza actually reduced to practice the invention of 2-amino-6-di-n-propylamino-4,5,6,7-tetrahydrobenzthiazole prior to June 19, 1985, the date that Dr. Laguzza signed the declaration for U.S. patent application Ser. No. 747,748. *See* BARR027413-14.

75. I note that Dr. Laguzza purportedly made this compound as the HBr salt ("Compound 188305") on or about December 6, 1983 and that it was tested for activity as a dopaminergic agent and as a hypotensive agent in December 1983 and January 1984 by Dr. Richard Hahn and Mr. Edward Smalstig. *See* Exs. 11, 14-16; Hahn Dep. 26:1-15; Smalstig Dep.16:8-17:14.

76. Although Dr. Laguzza submitted Compound 188305 for testing, there is no indication what expectations he may have had regarding its biological activity. Moreover, I have seen no testimony from Dr. Laguzza that he was informed of the results of that testing, nor testimony from Dr. Hahn or Mr. Smalstig that they provided him this information. A handwritten note from Dr. Hahn to Dr. Laguzza (Exh. 14 at LLY 9) is undated, and there is no indication when it was prepared or if it was actually received by Dr. Laguzza.

77. The fact that Dr. Laguzza did not make any additional tetrahydrobenzthiazoles or pursued any further evaluation of Compound 188305 itself suggests that, regardless of his expectations or understanding of its biological activity, he did not consider the tetrahydrobenzthiazoles to be a fruitful series for further investigation.

78. I note that neither Dr. Laguzza nor Lilly is asserting that Dr. Laguzza "invented" 2-amino-6-di-n-propylamino-4,5,6,7-tetrahydrobenzthiazole before December 22, 1984. In my opinion, there is insufficient evidence to conclude that Dr. Laguzza actually reduced to practice the invention of that compound prior to June 19, 1985, the date that he signed the declaration for Lilly's U.S. patent application in which it is claimed. *See* BARR027413-14.

2-Amino-6-di-methylamino-4,5,6,7-tetrahydrobenzthiazole(Lilly Compound 197511) and 2-Methylamino-6-di-methylamino-4,5,6,7-tetrahydrobenzthiazole (Lilly Compound 178694)

79. Similarly, I see no evidence from the documents or deposition testimony from Lilly scientists that Mr. William Turner reduced to practice the invention of 2-amino-6-di-methylamino-4,5,6,7-tetrahydrobenzthiazole or 2-methylamino-6-dimethylamino-4,5,6,7-tetrahydrobenzthiazole prior to the date that Mr. Turner signed the declaration for U.S. patent application Ser. No. 747,748. *See* BARR027413-14.

80. On or about May 10, 1984, Mr. Turner synthesized 2-amino-6-dimethylamino-tetrahydrobenzthiazole·2HBr (Compound 197511) and on or about July 14, 1984, he synthesized 2-methylamino-6-dimethylamino-tetrahydrobenzthiazole (Compound 178694). *See* Exh. 30 at LLY 47-48. Although he was not part of the research group that was interested in "partial ergoline" structures as dopaminergic agents, he testified that he offered to make these compounds since he was working with similar chemical intermediates. *See* Turner Dep. 81:2-22. His testimony makes clear that he did not synthesize these compounds to follow up any

hypothesis or expectation on his part as to their biological activity. Moreover, there is no indication that Mr. Turner ever learned of any results from the testing of these compounds prior to his involvement in the submission of the U.S. patent application in which they were claimed. *See* Turner Dep. 109:17-111:16.

81. According to Lilly's internal database of test results, Compound 197511 was sent to an outside contractor, PanLabs, Inc., for a broad panel of biological tests. Exh. 19, LLY 19; Turner Dep. 100:24-101:18. The data record shows that Compound 197511 was reported to be "active" in PanLabs, Inc. Test No. 1057; however, the identity of that test is not indicated. The data record also shows that the results were not obtained until January 30, 1985. In other words, the earliest that the invention of Compound 197511 could have been reduced to practice is January 30, 1985, even if Turner had received that information and understood its significance.

82. The same data record indicates that Compound 178694 did not show any activity in a battery of biological tests, the earliest record for which was October 9, 1985. Exh. 19, LLY 39; Turner Dep. 103:12-109:10. Thus, the invention of this compound could not have been reduced to practice prior to this date, if then.

83. In summary, the evidence shows that the earliest date at which Mr. Turner could be said to have reduced to practice the invention of 2-amino- and 2-methylamino-6-di-methyl-amino-4,5,6,7-tetrahydrobenzthiazole is June 19, 1985, the date that he signed the declaration for Lilly's U.S. patent application claiming these compounds. *See* BARR027413-14.

N. CONCLUSIONS

84. In my opinion, Barr and its expert Dr. Anslyn have not made valid arguments with regard to the disputed claims in the '812 Patent regarding adequate description in the German priority document or prior invention by Lilly. I believe that Dr. Anslyn's opinion on

adequate description is based on an inappropriate analysis of the disclosure of the priority document. Moreover, the evidence that I have reviewed does not provide any support for the premise that the Lilly scientists were in possession of the invention relating to the disputed claims prior to June 19, 1985. Barr's arguments are unconvincing and fall short of the standards of clear and convincing evidence that I understand must apply.

85. In forming his opinion that the German '075 priority application did not disclose halogenated phenyl groups as part of the R_1 substituents, Dr. Anslyn has focused narrowly on the definition of the genus of compounds in Claim 1. He has not, as I understand the law requires, properly analyzed the application as a whole, which not only discloses synthetic methods that produce those compounds but also describes starting materials and synthetic intermediates that would reasonably lead one of skill in the art to them.

86. The synthetic methods disclosed in the German '075 application are more than adequate to lead one of ordinary skill without difficulty to diaminotetrahydrobenzthiazoles containing halogenated phenyl groups as part of the R_1 substituents. No new methods or synthetic chemistry was required to obtain the additional compounds embraced in the genus of the '812 Patent. This opinion is confirmed by the fact that Lavall applied, without any difficulty at all, the methods outlined in the German priority applications to make five such compounds. The specification of the German priority applications thus provided satisfactory written description to support the genus claims of the '812 Patent.

87. In conclusion, I disagree with Dr. Anslyn's opinion that "that there is nothing in either of the German applications that discloses implicitly or explicitly to the skilled artisan, any starting material, intermediate, or final product in which R_1 contains or optionally contains a halogenated phenyl group." In my opinion, the German priority applications adequately disclose

to one of skill in the art the halogenated phenyl alkyl R_1 derivatives to meet the written description requirement.

88. In addition to Barr's failure to show actual reduction to practice by clear and convincing evidence, my analysis of the evidence concerning the work performed at Lilly by Dr. Laguzza and Mr. Turner shows that it does not constitute invention of 2-amino-6-dipropylamino-4,5,6,7-tetrahydrobenzthiazole, 2-amino-6-di-methylamino-4,5,6,7-tetrahydrobenzthiazole, and 2-methylamino-6-di-methylamino-4,5,6,7-tetrahydrobenzthiazole prior to June 19, 1985, the date that Dr. Laguzza and Mr. Turner signed the declaration for Lilly's U.S. patent application in which it is claimed.

O. OTHER MATTERS

89. I may rely on visual aids and demonstrative exhibits that illustrate the basis for my opinion. Examples of these visual aids and demonstrative exhibits may include, for example, diagrams of one or more of the compounds claimed, and blow-ups of documents considered or excerpts from this report.

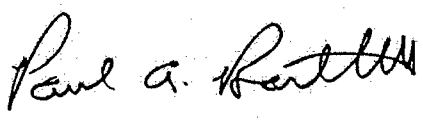
90. My opinions are based upon the information that I have considered to date. I reserve the right to supplement or amend my opinions in response to opinions (including any rebuttal opinions) expressed by Barr's experts or in light of any additional evidence, testimony, or other information that may be provided to me after the date of this report, including at trial.

91. I am being compensated for my time in this matter at my standard hourly consulting rate of $700 per hour, or $7,000 per day for travel outside California. No part of my compensation is dependent on the outcome of this litigation.

92. In the last four years, I have testified as an expert by affidavit in Aventis Pharma, Inc., Aventis Pharma Deutschland GmbH, and Schering Corp. v. Novopharm, Ltd. (Canadian

Federal Court File No. T-1965-05), in Warner-Lambert v. Ranbaxy (U.S. District of NJ, 00-CV-2931), in Sanofi-Aventis Canada, Inc. v. Cobalt Pharmaceuticals, Inc. (Canadian Federal Court File No. T-1710-06), in Sanofi-Aventis Canada, Inc. v. Pharmascience, Inc. (Canadian Federal Court File No. T-2300-06), in Monsanto Technology LLC v. Cargill International SA (United Kingdom High Court of Justice file HC 2006 C00585), in Greta Murphy et al. v. Merck & Co., Inc. (U.S. Southern Dist. NY No. 1:06-md-1789 JFK), and in Novartis Pharmaceuticals Corp. et al. v. Teva Pharmaceuticals USA, Inc. (U.S. District of NJ: 05-1887 DMC); by affidavit and deposition in Novartis Pharmaceuticals Corp. et al. v. Dr. Reddy's Laboratories (U.S. Southern District of NY, 02 Civ. 5560), in Bristol-Myers Squibb Canada Co. and Kyorin Pharmaceutical co., Ltd. v. Novopharm, Ltd. (Canadian Federal Court File No. T-1070-04), in Aventis Pharma, Inc., Aventis Pharma Deutschland GmbH, and Schering Corp. v. Laboratoire Riva, Inc. (Canadian Federal Court File No. T-1384-04), in Astra-Zeneca v. KV Pharmaceuticals et al. (U.S. Eastern District of MO, 04-CV-0800); and in Eli Lilly Canada v. Novopharm, Ltd. (Canadian Federal Court File No. T-1770-05); and by affidavit and at trial in Merck, Merck-Frosst Canada & Astra-Zeneca v. Apotex-Canada (Canadian Federal Court File No. T-2972-96), in Synthon IP, Inc. v. Pfizer, Inc. (U.S. District Court, Eastern District of VA, 1:05cv01267), in Janssen-Ortho Inc. and Daiichi Pharmaceutical Co., Ltd. v. Novopharm Ltd. (Canadian Federal Court File No. T-2175-04), and in GlaxoSmithKline v. Teva Pharmaceuticals USA, Inc. (U.S. District Court, Delaware, No. 05-197-GMS)

Dated: May 17, 2007



Paul A. Bartlett

EXHIBIT A

Paul A. BARTLETT

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birthdate January 5, 1948

education Harvard University: A.B. and A.M. (Chemistry), 1969
[with Prof. David Dolphin]
Stanford University: Ph.D. (Chemistry), 1972
[with Prof. William S. Johnson]
University of California, San Diego: Postdoctoral Fellow, 1972-73 [with Prof. S. Jonathan Singer]
Max-Planck-Institut für exp. Medizin, Göttingen: Sabbatical, 1981 [with Prof. Fritz Eckstein]
Max-Planck-Institut für Biochemie, Martinsried: Sabbatical, 1988 [with Prof. Robert Huber]

academic positions University of California, Berkeley
Assistant Professor, 1973-79, Associate Professor, 1979-82, Professor, 1982-2003, Emeritus
Department of Chemistry, Vice-Chair 1980-84, Chair, 1996-2000
Committee on Budget & Interdepartmental Relations: Member, 1985-87; Chair 1989-90
Academic Planning Board Advisory Panel for Biosciences, Chair 1993
Executive Vice Chancellor Search Committee, Chair 1999
Center for New Directions in Organic Synthesis, Director 1999-2005

professional positions National Institutes of Health: Bioorganic and Natural Products Study Section (1984-87);
National Advisory General Medical Sciences Council (*ad hoc* member 1989); Proteomics, Protein Expression & Protein Therapeutics Special Study Section (*ad hoc* member, 2003)
Editorial Advisory Boards: J. Org. Chem. (1985-90), Bull. Soc. Chim. Fr. (1985-92), Drug Discovery Today (1996-98), Molecular Medicine (1994-98), Molecules (1995-2000), J. Comb. Chem. (1998-2001), Chemistry & Biology (1993-2003), Organic Letters (1999-), ChemMedChem (2005-)
1987 American Chemical Society, National Organic Symposium Executive Officer
1987 Gordon Conference on Enzymes, Coenzymes, and Metabolic Pathways, Co-Chair
1989 Enzyme Mechanisms Conference, Chair
1993 Gordon Conference on Bioorganic Chemistry, Co-Chair
XVth International Symposium on Medicinal Chemistry Advisory Committee (1998)
2001 Keystone Symposium: "Impact of Genomics on Drug Discovery & Development", Co-Chair
2004 Keystone Symposium: "New Advances in Drug Discovery & Development", Co-Chair
2006 Keystone Symposium: "Structure-Based Drug Design", Co-Chair

honors and awards National Science Foundation Predoctoral Fellow, 1969-72
National Institutes of Health Postdoctoral Fellow, 1972-73
Alfred P. Sloan Research Fellow, 1979-81
Alexander von Humboldt Foundation, Fellow, 1981, Senior Scientist Award, 1988
Miller Professor, 1984-85, 1996
Stuart Pharmaceuticals Award, 1987
NIH MERIT Award, 1988
Buck Whitney Medal, Eastern New York ACS, 1989
Cope Scholar Award, American Chemical Society, 1990
American Academy of Arts and Sciences, Fellow, 1994
American Association for the Advancement of Science, Fellow, 1999
The Berkeley Citation, 2003

research Bioorganic chemistry: Design, synthesis, and evaluation of biologically active compounds

industrial positions -current Pharmacopeia, Co-Founder; Chair, Scientific Advisory Board 1993-; Board of Directors 1998-
Novartis Science Board, 2000-
SGX Pharmaceuticals, Scientific Advisory Board, 2003-
MannKind Corporation, Scientific Advisory Board, 2006-

industrial positions -past

Sterling-Winthrop Research Institute, Rensselaer, New York, chemist 1971
Bristol-Myers Company, consultant 1979-83
DuPont Central Research & Development, consultant 1980-87
FMC Corporation, consultant 1981-84
Schering-Plough Corporation, consultant 1984-96
Chevron Chemical Company - Ortho Division, consultant 1985-89
IGEN, Scientific Advisory Board, 1986-95
Celgene, Scientific Advisory Board, Member, 1987-91; Chair, 1991-96
Agouron Pharmaceuticals → Pfizer-La Jolla, Scientific Associate & consultant, 1987-88, 1992-2004
Chiron Corporation, Scientific Associate, 1988-93; consultant 2004-2005
SmithKline Beecham, Chemical Technologies Advisory Board, 1989-92
Sandoz Research Institute, Scientific Advisory Board, 1991-93; Chair, 1993
Molecular Simulations, Inc., Scientific Advisory Board, 1991-1999
Tularik → Amgen, Scientific Advisory Board, 1992-2006
Monsanto Company, consultant and Ceregen Scientific Advisory Board, 1994-97
Bristol-Myers Squibb, consultant 1997-99
Rosetta Inpharmatics, Scientific Advisory Board, 1997-2001
Argonaut, Scientific Advisory Board, 2000-2005

selected lectureships

G.D. Searle Symposium, Chemistry of Bioactive Substances, 1990
10th Annual Graduate Student Symposium for the Pharmacological Sciences, University of Michigan, keynote speaker, 1990
Merck-Frosst Lecturer, University of British Columbia, 1990
18th Peter A. Leermakers Symposium, Wesleyan University, 1990
Italian Advanced School of Organic Chemistry, Ischia, 1990
IVth Nagoya Conference on Frontiers of Organic Synthesis, 1990
Burroughs-Wellcome Lecturer, University of North Carolina, 1991
Robert A. Welch Foundation Lectureship, 1991
XXXIV Robert A. Welch Foundation Conference on Chemical Research Lecturer, 1991
Proctor & Gamble Lecturer, Massachusetts Institute of Technology, 1991
Frontiers in Chemistry Lecturer, Case Western Reserve, 1991
Fifth Annual Eli Lilly Grantee Symposium in Organic Chemistry, 1992
Chemistry as a Life Science Symposium Lecturer, Rutgers, 1992
Bio-Méga Lecturer, Université de Montréal, 1992
8th Conference of the Nozaki School, Yokohama, 1992
Interfaces Between Chemistry and Biology Symposium, Marion-Merrell-Dow Research Inst., 1993
W. S. Johnson Symposium, Harvard University, 1993
Frontiers in Chemistry, International Roche Pharma Meeting, Wildhaus, Switzerland, 1994
H. C. Brown Symposium, Purdue University, 1994
Rhône-Poulenc Rorer International Round Table, Turnberry, Scotland 1994
NATO Advanced Study Institute on Chemical Synthesis, Ravello, Italy, 1994
3ème Cycle en Chemie 'Synthesis - Methods and Goals', Champéry, Switzerland, 1994
Plenary Lecture, Gesell. deutsche Chem. Medicinal Chemistry meeting, Schliersee, 1994
Wyeth-Ayerst Lecturer, Columbia University, 1995
Syntex Lecturer, University of Colorado, Boulder, 1996
Contemporary Challenges in Molecular Medicine symp., Univ. of Michigan/Parke-Davis, 1996
Syntex Distinguished Lectureship, Colorado State University, 1997
2nd Lausanne Bioorganic Chemistry Symposium, Switzerland, 1997
Karcher Lecturer, University of Oklahoma, 1998
Pfizer Lecturer, SUNY Stony Brook, 1998
Plenary Lecture, XVth International Medicinal Chemistry Symposium, Edinburgh, 1998
Bio-Méga Lecturer, University of Alberta, 1999
Humphrey Memorial Symposium, University of Vermont, 1999
Plenary Lecture, Royal Society of Chemistry Symposium "Protease 2000"
Haverford College Distinguished Philip's Visitor, 2001
7th Symposium of the Bijvoet Graduate School for Biomolecular Chemistry, 2001
North Jersey ACS Organic Topical Group Symposium, 2003
Ernst Schering Research Foundation Lecturer, Berlin, 2003
Keystone Symposium on New Advances in Drug Discovery, Closing Address, 2004
Drug Design Symposium, Center for Cancer Experimental Therapeutics, Kansas University, 2006

recent publications

187. Hammond, M.C.; Harris, B.Z.; Lim, W.A.; Bartlett, P.A. β-Strand Peptidomimetics as Potent PDZ Domain Ligands" *Chem. Biol.* **2006**, *13*, 1247-1251.
184. Phillips, S.T.; Piersanti, G.; Bartlett, P.A. "Quantifying amino acid conformational preferences and side chain-side chain interactions in β-hairpins" *Proc. Natl. Acad. Sci. USA* **2005**, *102*, 13737-13742.
173. An, M.; Maitra, U.; Neidlein, U.; Bartlett, P.A."5-Enolpyruvylshikimate-3-Phosphate Synthase: Chemical Synthesis of the Tetrahedral Intermediate and Assignment of the Stereochemical Course of the Enzymatic Reaction" *J. Am. Chem. Soc.* **2003**, *125*, 12759-12767.
170. Spaller, M.R.; Thielemann, W.; Brennan, P.E.; Bartlett, P.A. "Combinatorial Synthetic Design. Solution and Polymer-Supported Synthesis of Heterocycles *via* Intramolecular Aza-Diels-Alder and Iminoalcohol Cyclizations" *J. Comb. Chem.* **2002**, *4*, 516-522.
167. Bartlett, P.A.; Yusuff, N.; Rico, A.C.; Lindvall, M.K. "Anti-Hydrophobic Solvent Effects: An Experimental Probe for the Hydrophobic Contribution to Enzyme-Inhibitor Binding", *J. Am. Chem. Soc.* **2002**, *124*, 3853-3857.
166. Phillips, S.T.; Rezac, M.; Abel, U.; Kossenjans, M.; Bartlett, P.A. "'@-Tides': The 1,2-Dihydro-3(6*H*)-pyridinone Unit as a ß-Strand Mimic", *J. Am. Chem. Soc.* **2002**, *124*, 58-66.
158. Khan, A.R.; Parish, J.C.; Fraser, M.E.; Smith, W.W.; Bartlett, P.A.; James, M.N.G. "Lowering the Entropic Barrier for Binding Conformationally Flexible Inhibitors to Enzymes" *Biochemistry*, **1998**, *37*, 16839-16845.
156. Smith, W.W.; Bartlett, P.A. "Macrocyclic Inhibitors of Penicillopepsin. 3. Design, Synthesis, and Evaluation of an Inhibitor Bridged Between P2 and P1'", *J. Am. Chem. Soc.* **1998**, *120*, 4622-4628.
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149. Marx, M.A.; Grillot, A.-L.; Louer, C.T.; Beaver, K.A.; Bartlett, P.A. "Synthetic Design for Combinatorial Chemistry. Solution and Polymer-Supported Synthesis of Polycyclic Lactams by Intramolecular Cyclization of Azomethine Ylides", *J. Am. Chem. Soc.* **1997**, *119*, 6153-6167.
135. Kozlowski, M. C.; Tom, N. J.; Seto, C. T.; Sefler, A. M.; Bartlett, P. A., "Chorismate-Utilizing Enzymes Isochorismate Synthase, Anthranilate Synthase and *p*-Aminobenzoate Synthase: Mechanistic Insight Through Inhibitor Design", *J. Am. Chem. Soc.* **1995**, *117*, 2128-2140.

seminal publications (100-600+ citations)

130. Nestler, H. P.; Bartlett, P. A.; Still, W. C. "A General Method for Molecular Tagging of Encoded Combinatorial Chemistry Libraries" *J. Org. Chem.* **1994**, *59*, 4723-4724.
126. Lauri, G.; Bartlett, P.A., "CAVEAT: A Program to Facilitate the Design of Organic Molecules", *J. Comp. Aided Mol. Design* **1994**, *8*, 51-66.
123. Simon, R. J.; Kania, R. S.; Zuckerman, R. N.; Huebner, V. D.; Jewell, D. A.; Banville, S.; Ng, S.; Wang, L.; Rosenberg, S.; Marlowe, C. K.; Spellmeyer, D.; Tan, R.; Frankel, A. D.; Santi, D. V.; Cohen, F. E.; Bartlett, P. A., "Peptoids: A Modular Approach to Drug Discovery", *Proc. Natl. Acad. Sci., USA* **1992**, *89*, 9367-9371.
110. Morgan, B.P.; Scholtz, J.M., Ballinger, M., Zipkin, I.; Bartlett, P.A., "Differential Binding Energy: A Detailed Evaluation of the Influence of Hydrogen-Bonding and Hydrophobic Groups on the Inhibition of Thermolysin by Phosphorus-Containing Inhibitors", *J. Am. Chem. Soc.* **1991**, *113*, 297-307.
90. Jackson, D.Y.; Jacobs, J.W.; Sugasawara, R.; Reich, S.H.; Bartlett, P.A.; Schultz, P.G., "An Antibody-Catalyzed Claisen Rearrangement", *J. Am. Chem. Soc.* **1988**, *110*, 4841-4842.
88. Bartlett, P.A.; McLaren, K.L.; Ting, P.C., "Radical Cyclization of Oxime Ethers", *J. Am. Chem. Soc.* **1988**, *110*, 1633-1634.
85. Bartlett, P.A.; Marlowe, C.K., "A Possible Role for Water Dissociation in the Slow Binding of Phosphorus-Containing Transition State Analog Inhibitors of Thermolysin", *Biochemistry* **1987**, *26*, 8553-8561.
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77. Bartlett, P.A.; Marlowe, C.K., "Evaluation of the Intrinsic Binding Energy from a Hydrogen Bonding Group in an Enzyme Inhibitor", *Science* **1987**, *235*, 569-571.
47. Bartlett, P.A.; Marlowe, C.K., "Phosphonamidates as Transition State Analog Inhibitors of Thermolysin", *Biochemistry* **1983**, *22*, 4618-4624.
21. Bartlett, P.A., "Stereocontrol in the Synthesis of Acyclic Systems: Application to Natural Product Synthesis", Tetrahedron Report #71, *Tetrahedron*, **1980**, *36*, 2-72.

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Berkeley, California 94720

1. Bartlett, P.A.; Johnson, W.S., "An Improved Reagent for the O-Alkyl Cleavage of Methyl Esters by Nucleophilic Displacement", *Tetrahedron Lett.* **1970**, 4459-62.
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3. Bartlett, P.A.; Johnson, W.S., "A Stereospecific Total Synthesis of Estrone via a Cationic Olefinic Cyclization", *J. Am. Chem. Soc.* **1973**, *95*, 7501-02.
4. Bartlett, P.A.; Brauman, J.I.; Johnson, W.S.; Volkmann, R.A., "Concerning the Mechanism of a Nonenzymic Biogenetic-like Olefinic Cyclization", *J. Am. Chem. Soc.* **1973**, *95*, 7502-04.
5. Ruoho, A.; Bartlett, P.A.; Dutton, A.; Singer, S.J., "A Disulfide-Bridge Bifunctional Imidoester as a Reversible Cross-Linking Reagent", *Biochem. Biophys. Res. Commun.* **1975**, *63*, 417.
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7. Bartlett, P.A.; Long, K.P., "A New Class of Potential Photoaffinity Labels. α-Diazophosphonic Acids: Synthesis and Stability", *J. Am. Chem. Soc.* **1977**, *99*, 1267-1268.
8. Bartlett, P.A.; Green, F.R. III; Webb, T.R., "A Mild, Oxidative Nitro-to-Carbonyl Conversion and a New Prostaglandin Synthon", *Tetrahedron Lett.* **1977**, 331-334.
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10. Bartlett, P.A.; Myerson, J., "Stereoselective Epoxidation of Acyclic Olefinic Carboxylic Acids via Iodolactonization", *J. Am. Chem. Soc.* **1978**, *100*, 3950-3952.
11. Bartlett, P.A.; Green, F.R. III; Rose, E.H., "The Synthesis of Acetylenes from Carboxylic Acid Derivatives via β-Ketosulfones", *J. Am. Chem. Soc.* **1978**, *100*, 4852-4858.
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13. Bartlett, P.A.; Bauer, B.; Singer, S.J., "Synthesis of Water-Soluble Undecagold Cluster Compounds of Potential Importance in Electron Microscopic and other Studies of Biological Systems", *J. Am. Chem. Soc.* **1978**, *100*, 5085-5089.
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15. Summerton, J.E.; Bartlett, P.A., "Affinity Crosslinking Agents for Nucleic Acids: Use of 6-Bromo-5,5-dimethoxyhexanohydrazide for Crosslinking Cytidine to Guanosine and Crosslinking RNA to Complementary Sequences of DNA", *J. Mol. Biol.* **1978**, *122*, 145-162.
16. Summerton, J.E.; Bartlett, P.A., "Nucleic Acid Crosslinking Agent and Affinity Inactivation of Nucleic Acids Therewith", U.S. Patent 4,123,610 (October 31, 1978).
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18. Bartlett, P.A.; Hunt, J.T.; Adams, J.L.; Gehret, J.-C., "Phosphorus-Containing Purines and Pyrimidines: A New Class of Transition State Analogs", *Bioorganic Chem.* **1978**, *7*, 421-436.
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21. Bartlett, P.A., "Stereocontrol in the Synthesis of Acyclic Systems: Application to Natural Product Synthesis", Tetrahedron Report #71, *Tetrahedron*, **1980**, *36*, 2-72.
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Hediger, M.E. "Design, synthesis, and evaluation of aza inhibitors of chorismate mutase" *Bioorg. Med. Chem.* **2004**, *12*, 4995-5010 (DOI: 10.1016/j.bmc.2004.06.037)

EXHIBIT B

MATERIALS REVIEWED

Patent Prosecution Files

U.S. Patent No. 4,731,374
U.S. Patent No. 4,843,086
U.S. Patent No. 4,886,812

Deposition Transcripts

July 5, 2006 Bennett Laguzza deposition
July 6, 2006 William Turner deposition
July 7, 2006 Richard Hahn deposition
July 27, 2006 Barry Smalstig deposition
October 9, 2006 Joachim Mierau deposition and exhibits
October 19, 2006 Walter Kobinger deposition and exhibits
October 24, 2006 Rudolph Hurnaus deposition and exhibits
November 28, 2006 Dieter Hinzen deposition and exhibits
December 12, 2006 Gunter Schingnitz deposition and exhibits

Deposition Exhibits

Exhibit 1-51, 53

Production Documents

BARR 000662-666
BARR 027413-27414
BARR 209351-209403
BOE 00000712-746
BOE 00004078-4083
BOE 00004157-4166
BOE 00004167-4177
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BOE 00849191-849203
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BOE 00849164-849170
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Miscellaneous

July 1, 1997 FDA approval letter for Mirapex®